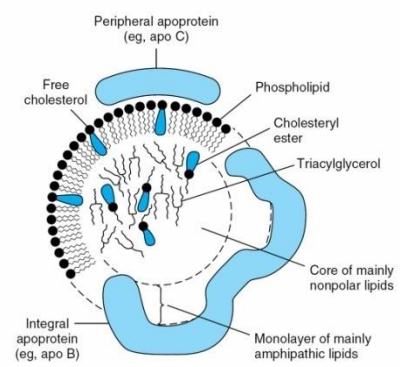
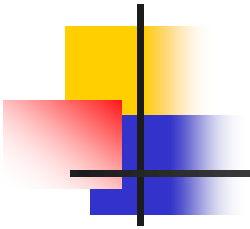
Lipid Transport and Storage



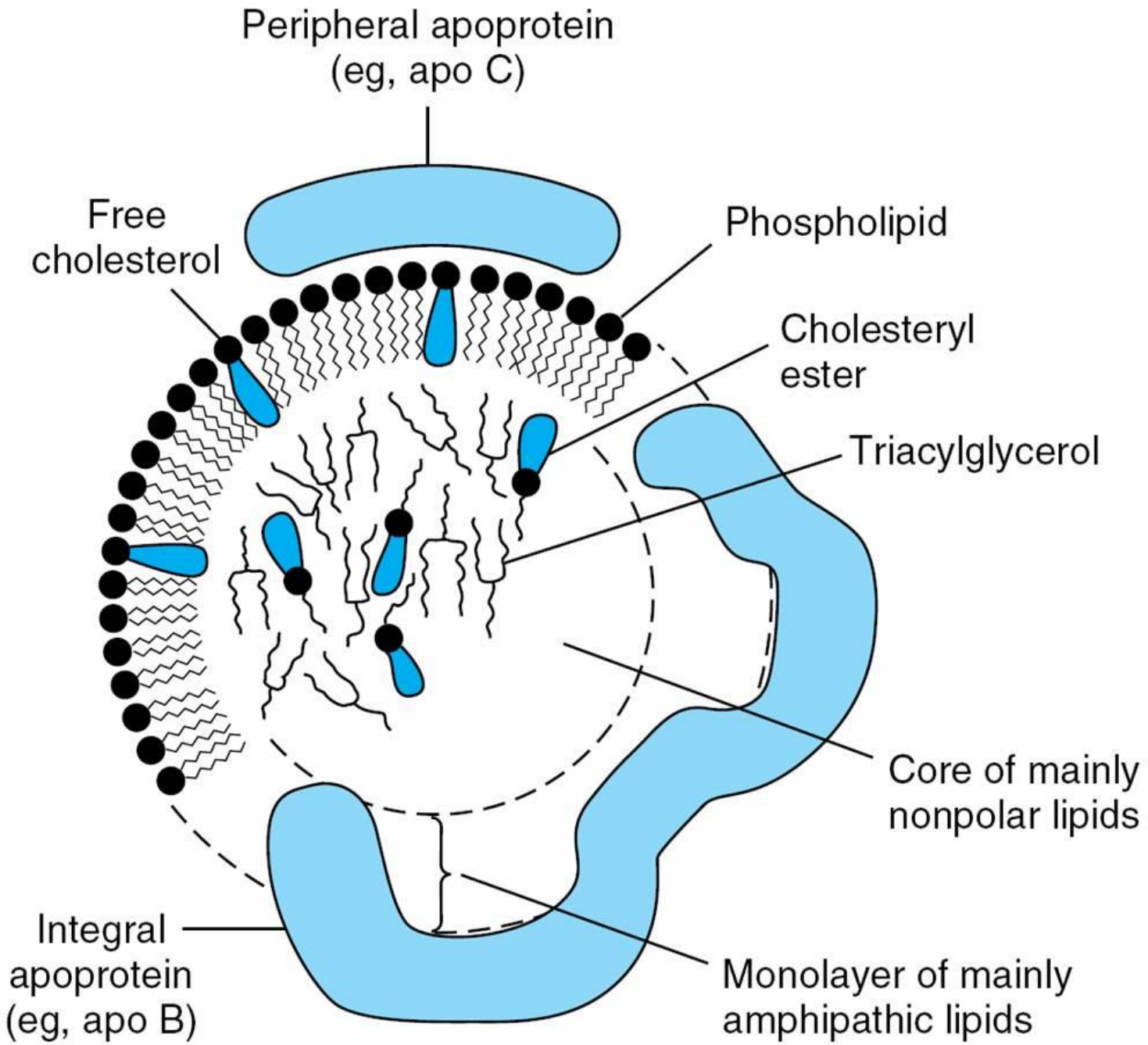
LIPIDS ARE TRANSPORTED IN THE PLASMA AS LIPOPROTEINS

- **Lipoproteins Consist of a Nonpolar Core & a Single Surface Layer of Amphipathic Lipids**
- **The Distribution of Apolipoproteins Characterizes the Lipoprotein**



- **FREE FATTY ACIDS** ARE RAPIDLY METABOLIZED

- **TRIACYLGLYCEROL** IS TRANSPORTED FROM THE INTESTINES IN CHYLOMICRONS & FROM THE LIVER IN VERY LOW DENSITY LIPOPROTEINS


Peripheral apoprotein
(eg, apo C)
Free
cholesterol
Phospholipid
Cholesteryl
ester
Triacylglycerol
Core of mainly
nonpolar lipids
Integral
apoprotein
(eg, apo B)
Monolayer of mainly
amphipathic lipids

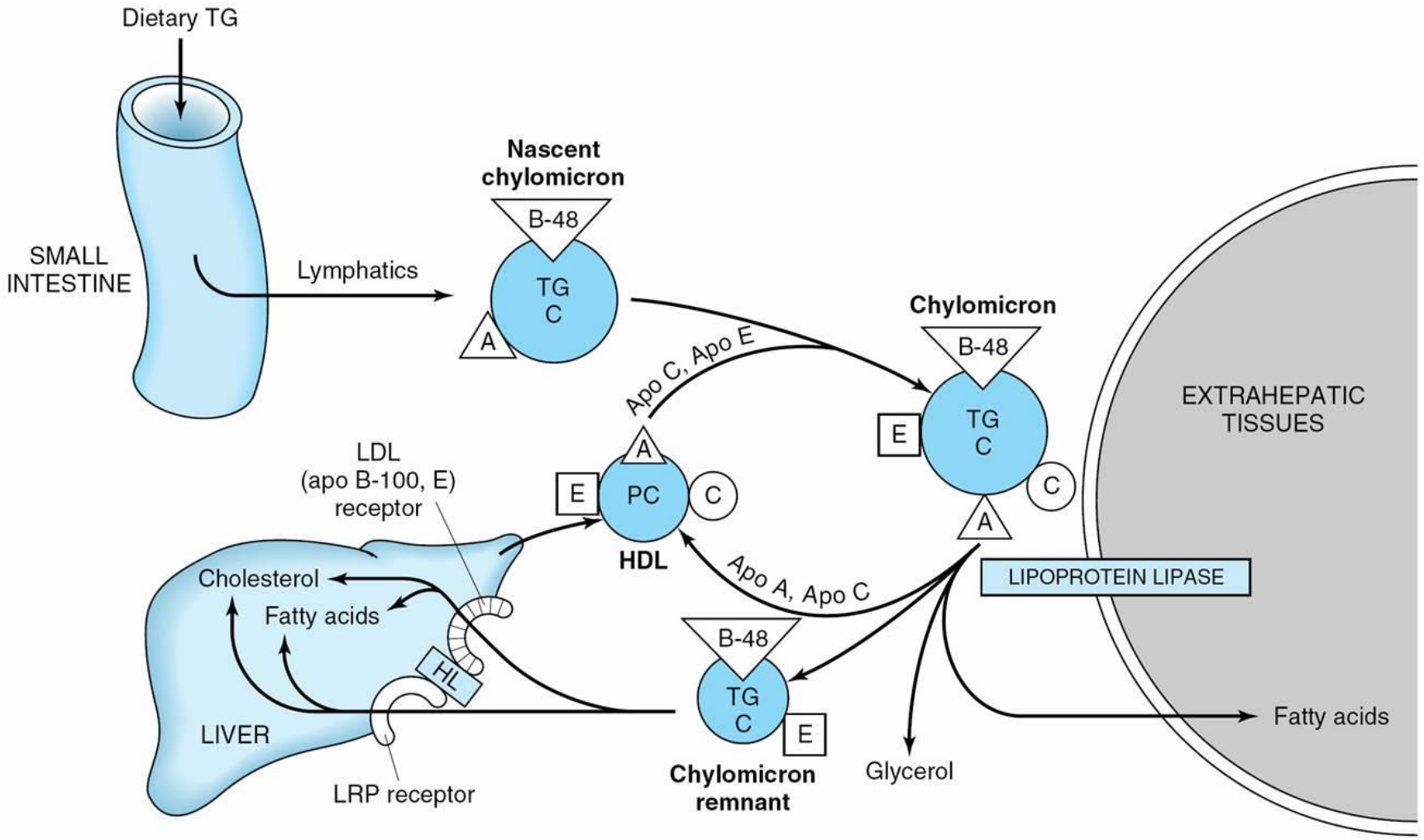
Composition of the **lipoproteins** in plasma of humans.

Lipoprotein	Source	Diameter (nm)	Density (g/mL)	Composition		Main Lipid Components	Apolipoproteins
				Protein (%)	Lipid (%)		
Chylomicrons	Intestine	90–1000	< 0.95	1–2	98–99	Triacylglycerol	A-I, A-II, A-IV,[1] B-48, C-I, C-II, C-III, E
Chylomicron remnants	Chylomicrons	45–150	< 1.006	6–8	92–94	Triacylglycerol, phospholipids, cholesterol	B-48, E
VLDL	Liver (intestine)	30–90	0.95–1.006	7–10	90–93	Triacylglycerol	B-100, C-I, C-II, C-III
IDL	VLDL	25–35	1.006–1.019	11	89	Triacylglycerol, cholesterol	B-100, E
LDL	VLDL	20–25	1.019–1.063	21	79	Cholesterol	B-100
HDL	Liver, intestine, VLDL, chylo-microns					Phospholipids, cholesterol	A-I, A-II, A-IV, C-I, C-II, C-III, D,[2] E
HDL_1		20–25	1.019–1.063	32	68		
HDL_2		10–20	1.063–1.125	33	67		
HDL_3		5–10	1.125–1.210	57	43		
Preβ-HDL[3]		< 5	> 1.210				A-I
Albumin/free fatty acids	Adipose tissue		> 1.281	99	1	Free fatty acids	

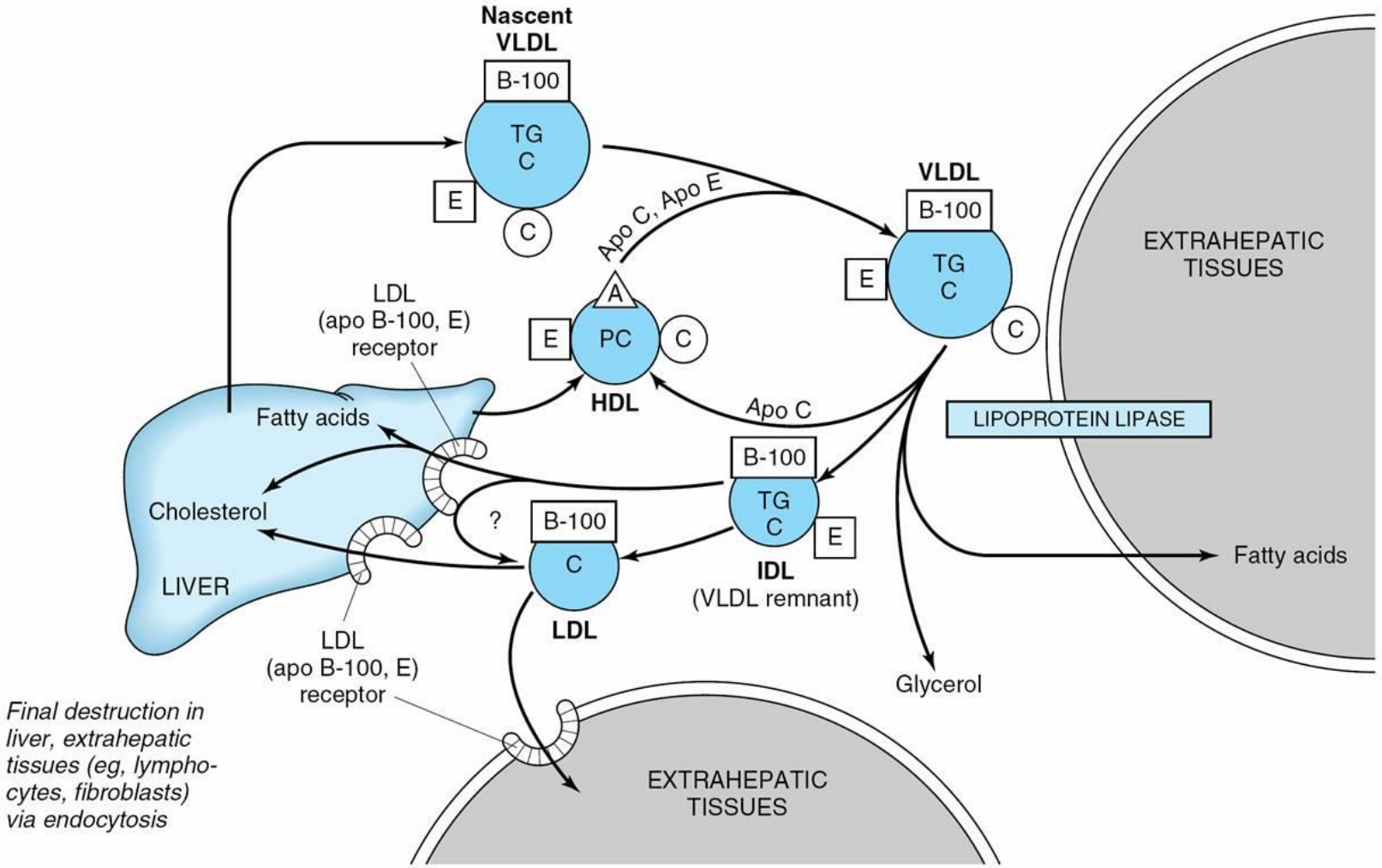
CHYLOMICRONS & **VLDL** ARE RAPIDLY CATABOLIZED

- *Triacylglycerols of Chylomicrons & VLDL Are Hydrolyzed by* ***Lipoprotein Lipase***
- *The Action of Lipoprotein Lipase Forms* ***Remnant Lipoproteins***
- *The* ***Liver*** *Is Responsible for the Uptake of Remnant Lipoproteins*

Metabolic fate of **chylomicrons**

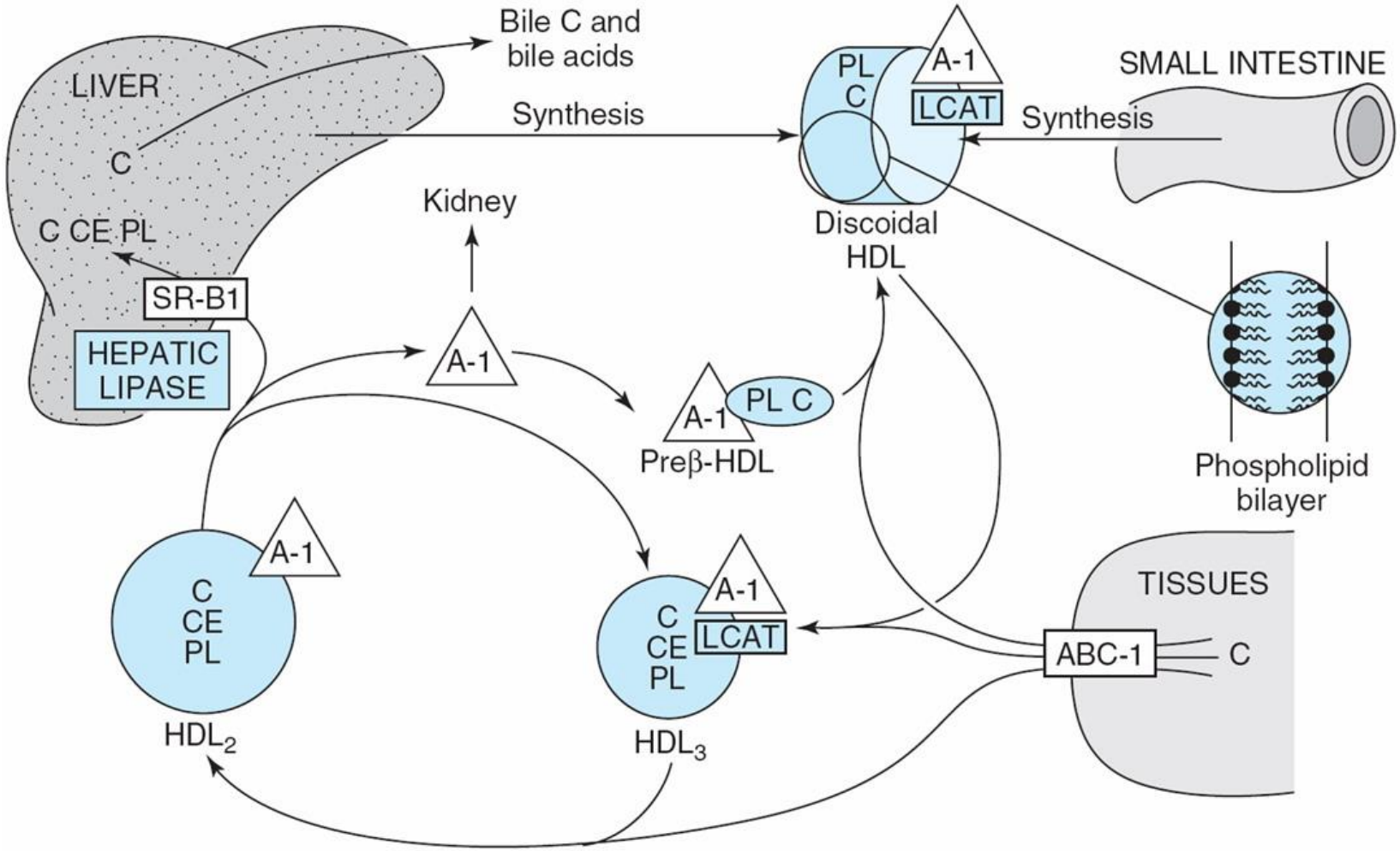


Metabolic fate of **VLDL** and production of **LDL**



- **LDL** IS METABOLIZED VIA THE **LDL RECEPTOR**

HDL TAKES PART IN BOTH LIPOPROTEIN **TRIACYLGLYCEROL** & **CHOLESTEROL** METABOLISM



CLINICAL ASPECTS

- **Imbalance in the Rate of TG Formation & Export Causes *Fatty Liver***

- **Ethanol Also Causes *Fatty Liver***

Lecithin cholesterol acyltransferase (LCAT)

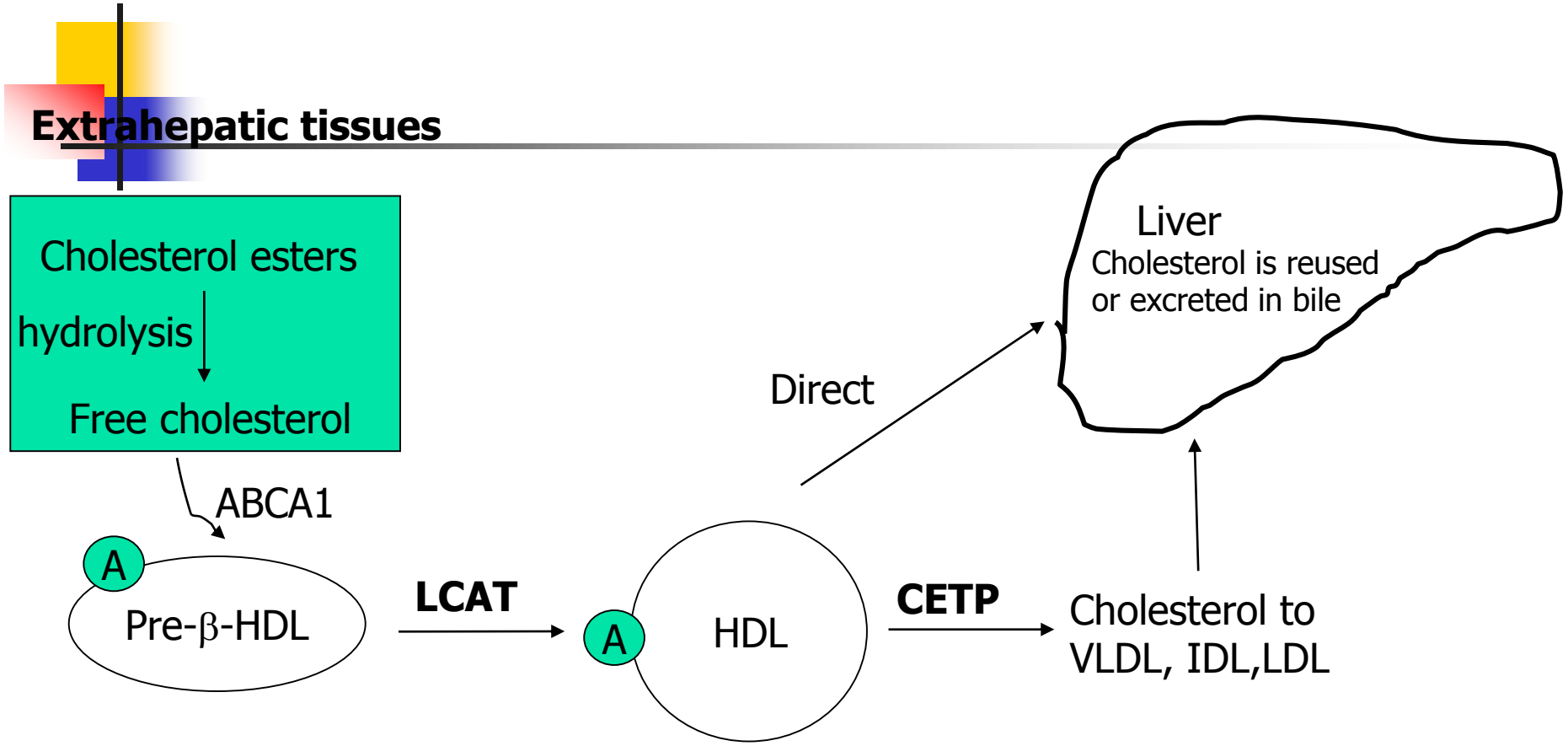
Secreted from liver into plasma, bound predominantly to HDL
LCAT catalyses:

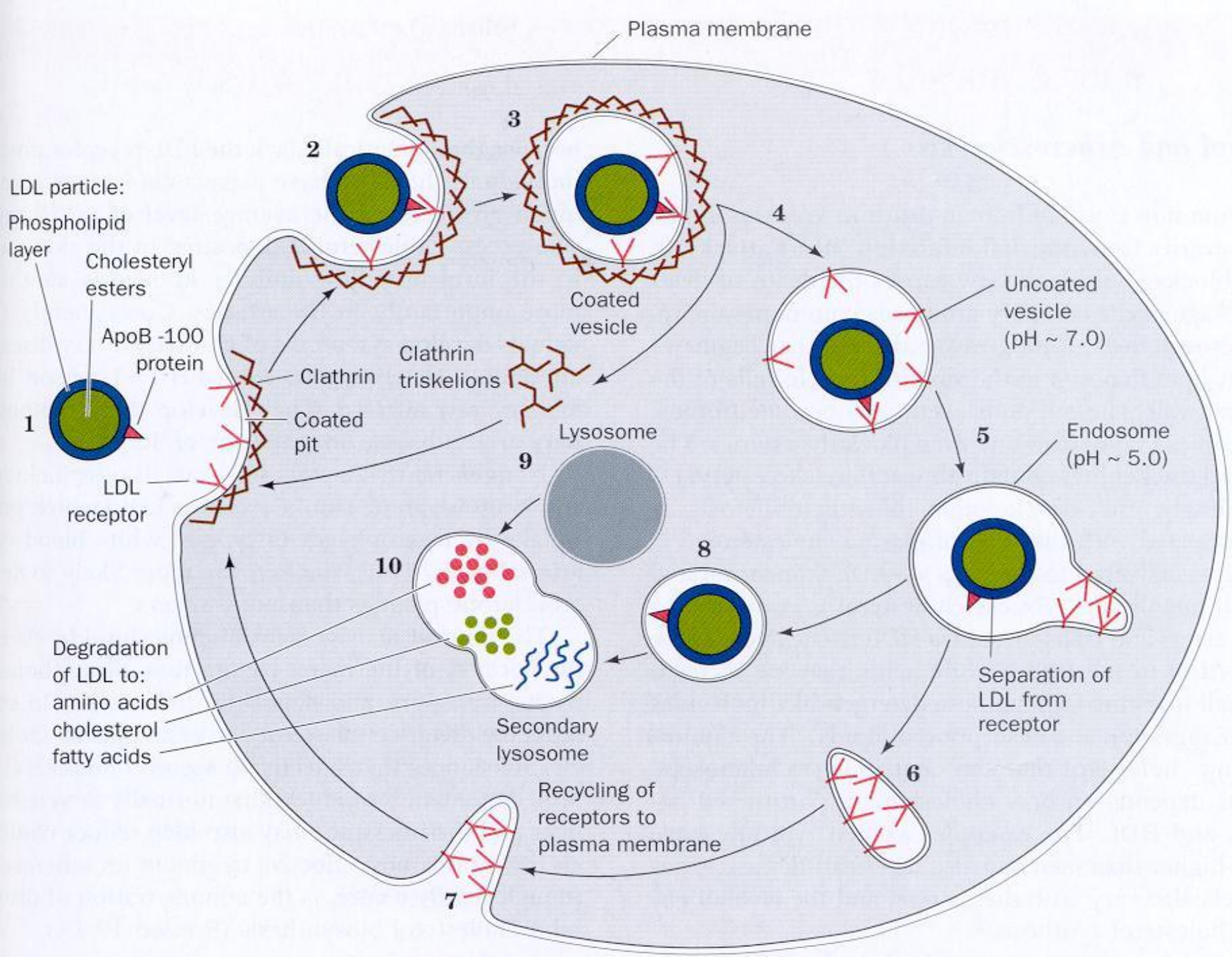
1) a transesterification reaction in which an acyl group from the 2-position of phosphatidylcholine (PC) is transferred to the 3-hydroxyl group of cholesterol (PC$\rightarrow$lyso-PC and FC $\rightarrow$ CE)

2) a lyso-PC acyltransferase reaction in which a fatty acid is transferred to lyso-PC, converting it to PC

LCAT activated by apoA-I

Reverse Cholesterol Transport: Indirect




Plasma membrane
LDL particle:
Phospholipid layer
Cholesteryl esters
ApoB -100 protein
1
LDL receptor
Coated pit
Clathrin
2
3
Coated vesicle
Clathrin triskelions
4
Uncoated vesicle (pH ~ 7.0)
5
Endosome (pH ~ 5.0)
Separation of LDL from receptor
6
Recycling of receptors to plasma membrane
7
8
9
Lysosome
10
Secondary lysosome
Degradation of LDL to:
amino acids
cholesterol
fatty acids

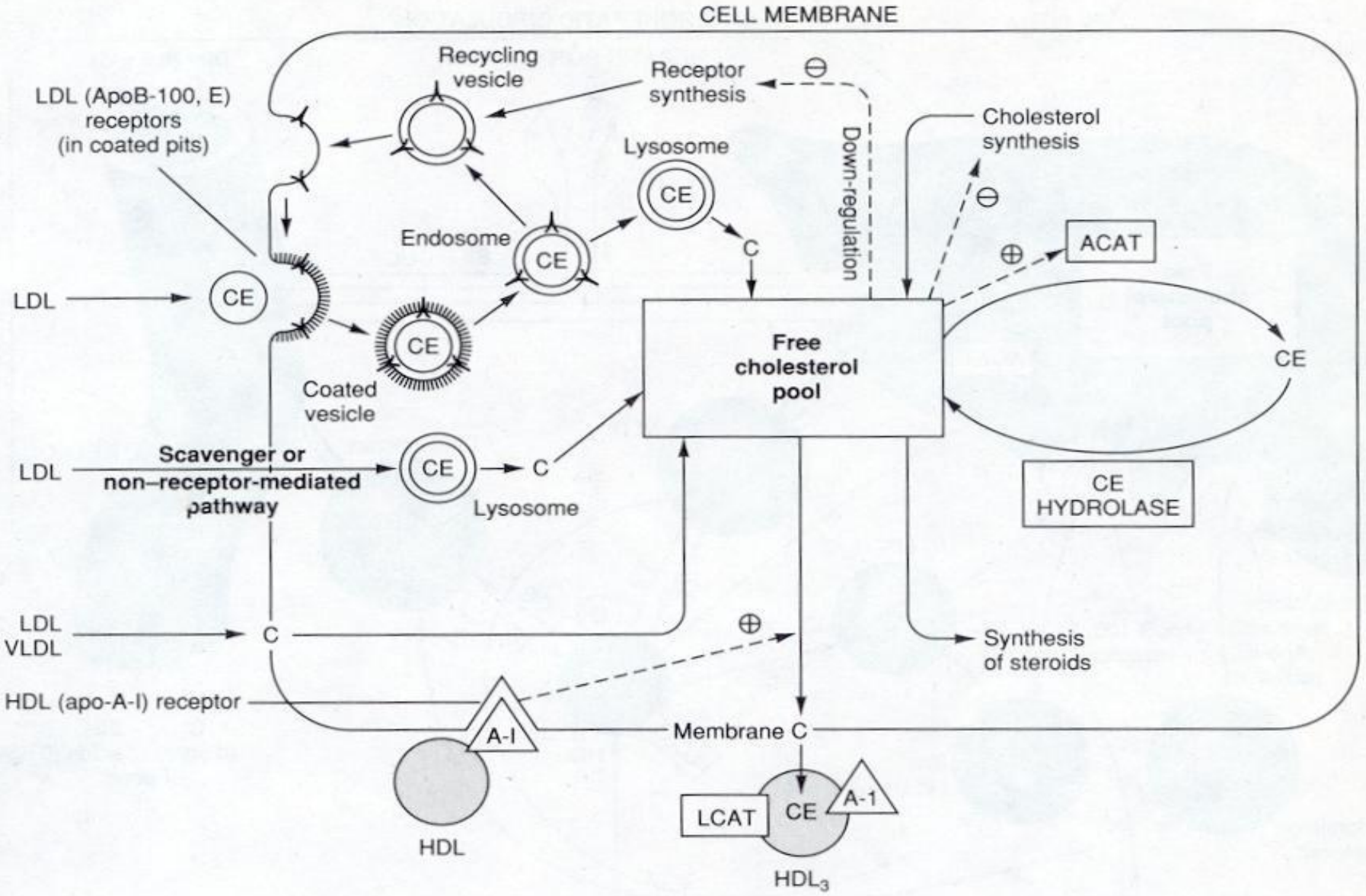
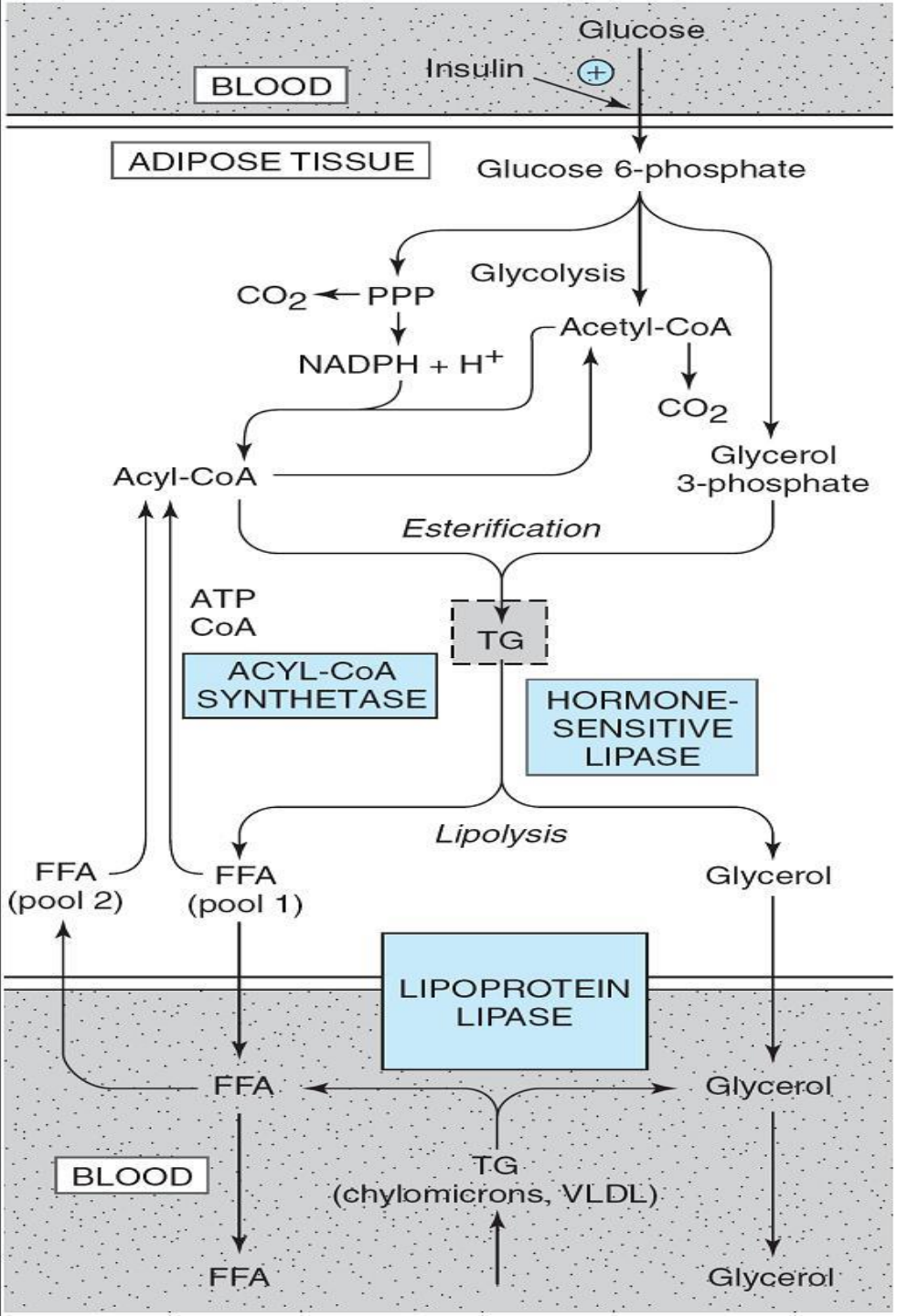


Figure 28–5. Factors affecting cholesterol balance at the cellular level. Reverse cholesterol transport may be initiated by HDL binding to an HDL (apo-A-I-) receptor, which via protein kinase C (see p 496), stimulates translocation of cholesterol to the plasma membrane. C, cholesterol; CE, cholesteryl ester; ACAT, acyl-CoA: cholesterol acyltransferase; LCAT, lecithin:cholesterol acyltransferase; A-1, apoprotein A-1; LDL, low-density lipoprotein; VLDL, very low density lipoprotein. LDL and HDL are not shown to scale.

ADIPOSE TISSUE IS THE MAIN STORE OF **TG** IN THE BODY

- The Provision of ***Glycerol 3-Phosphate*** Regulates Esterification: Lipolysis Is Controlled by **Hormone-Sensitive Lipase** (Figure 25–7)

- Increased **Glucose** Metabolism Reduces the Output of Free Fatty Acids


Glucose
Insulin
+
BLOOD
ADIPOSE TISSUE
Glucose 6-phosphate
Glycolysis
CO_2 ← PPP
Acetyl-CoA
NADPH + H^+
CO_2
Acyl-CoA
Glycerol 3-phosphate
Esterification
ATP
CoA
TG
ACYL-CoA SYNTHETASE
HORMONE-SENSITIVE LIPASE
Lipolysis
FFA (pool 2)
FFA (pool 1)
Glycerol
LIPOPROTEIN LIPASE
FFA
Glycerol
BLOOD
TG (chylomicrons, VLDL)
FFA
Glycerol

HORMONES REGULATE FAT MOBILIZATION

- **Insulin** Reduces the Output of Free Fatty Acids
- **Several Hormones** Promote Lipolysis

Lipolysis increased by:

- Epinephrine
- Norepinephrine
- Glucagon
- ACTH
- TSH
- Thyroid hormone
- GH
- MSH
- Vasopressin
- Caffeine
- Theophylline
- Leptin

Lipolysis decreased by:

- Insulin
- Nicotinic acid
- Prostaglandin E_1

BROWN ADIPOSE TISSUE PROMOTES THERMOGENESIS

- Brown adipose tissue is involved in metabolism particularly at times when **heat** generation is necessary
- Though not a prominent tissue in humans, it is present in normal individuals, where it could be responsible for **"diet-induced thermogenesis."**
- It is noteworthy that brown adipose tissue is reduced or absent in obese persons.

The tissue is characterized by:

- well-developed **blood** supply
- high content of **mitochondria** and **cytochromes**
- but **low activity** of ATP synthase.
- A thermogenic uncoupling protein, **thermogenin**, acts as a proton conductance pathway dissipating the electrochemical potential across the mitochondrial membrane

Thermogenesis increased by:

- **Norepinephine**
- **FFA**
- **Acyl-CoA**

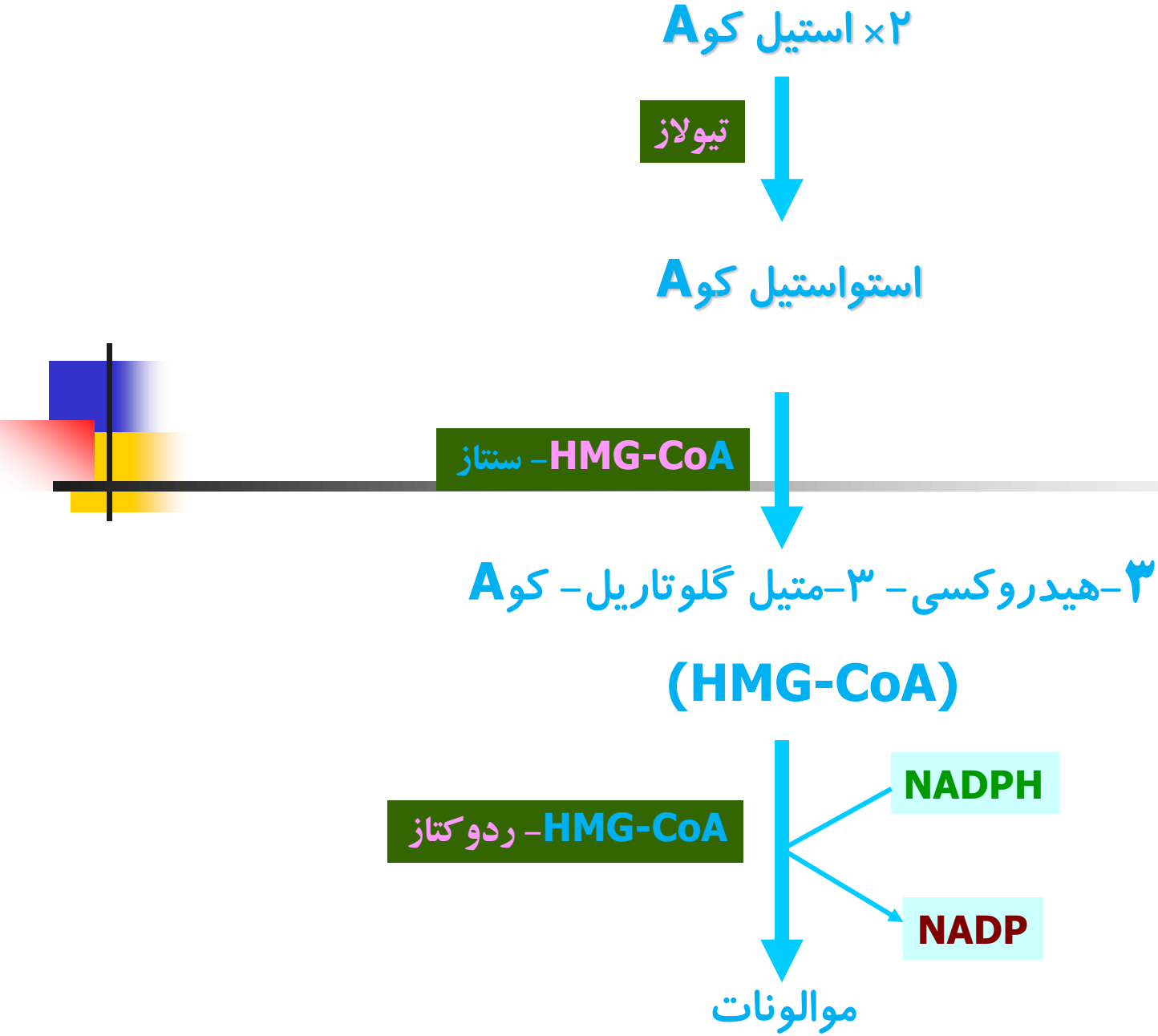
Thermogenesis decreased by:

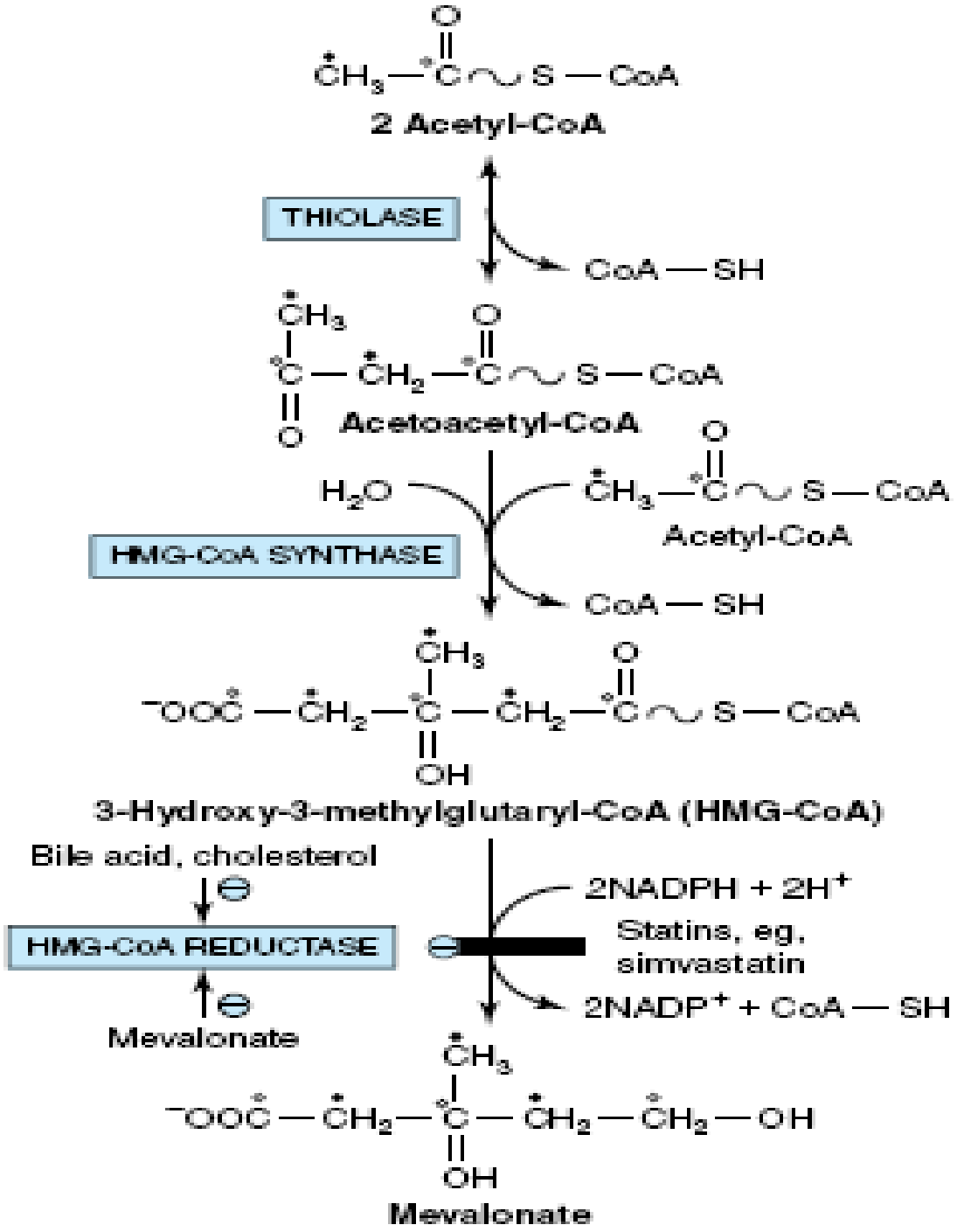
- **Purine nucleotides**

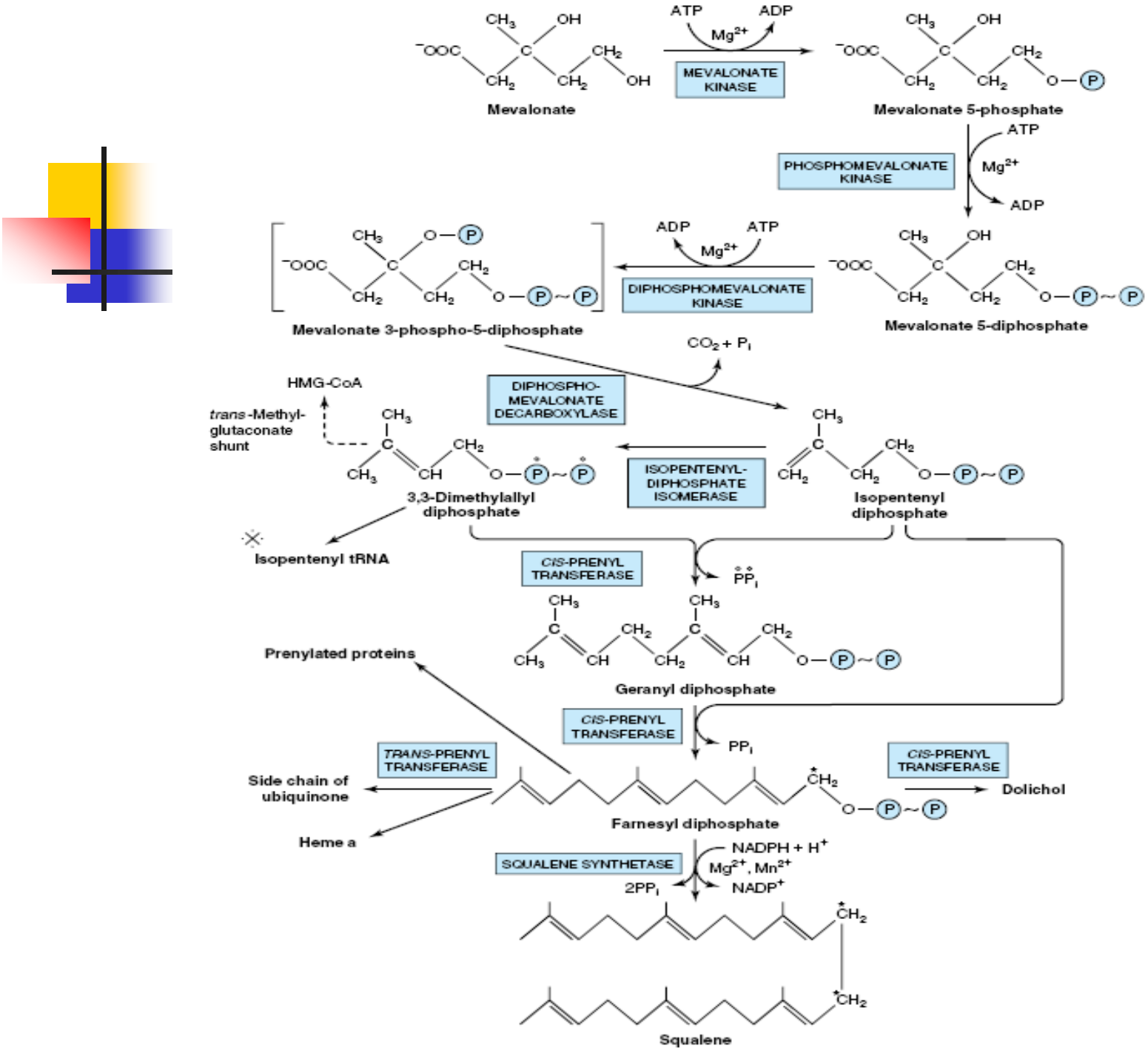
Cholesterol Metabolism

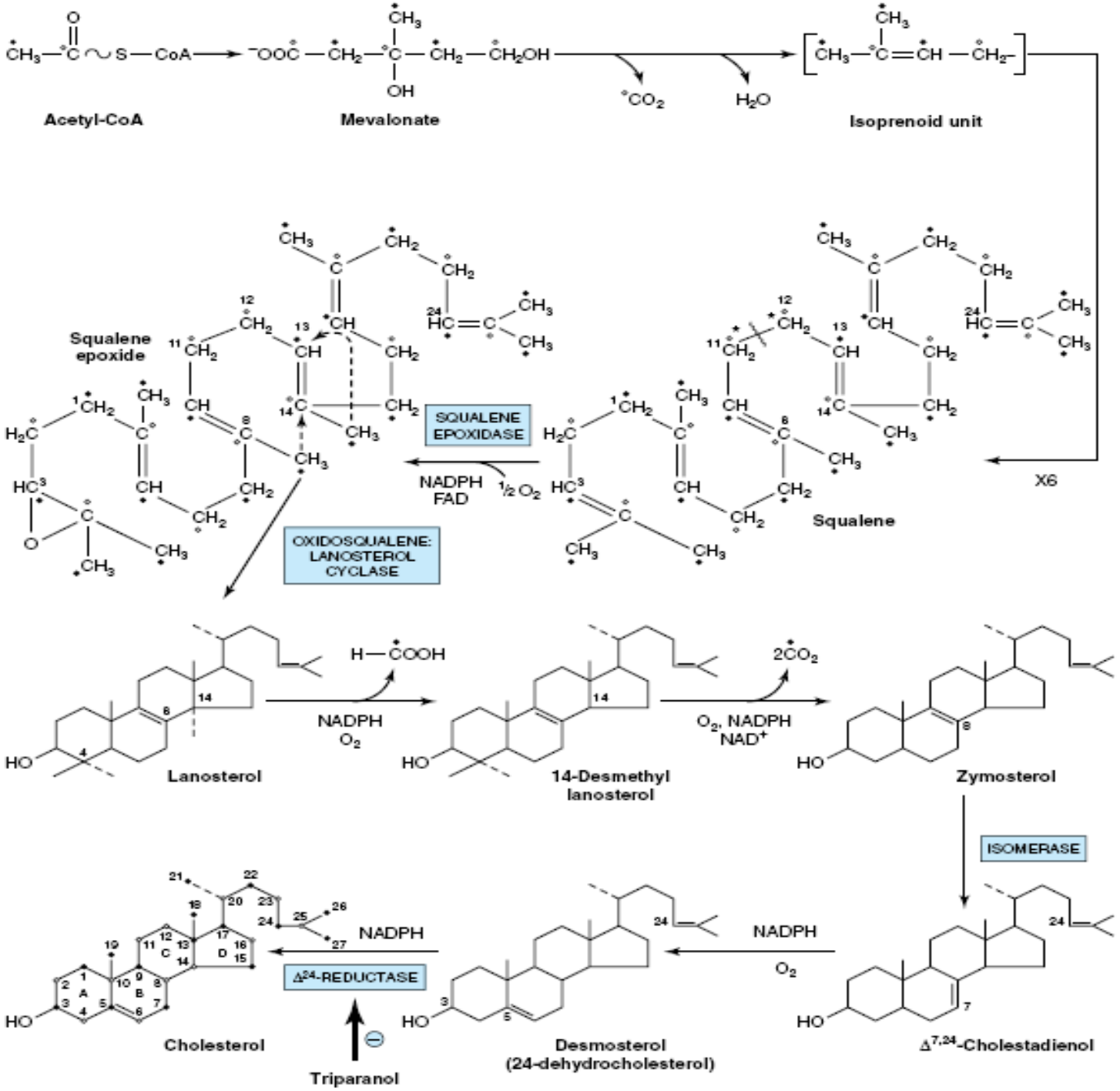
Biosynthesis of cholesterol into five steps

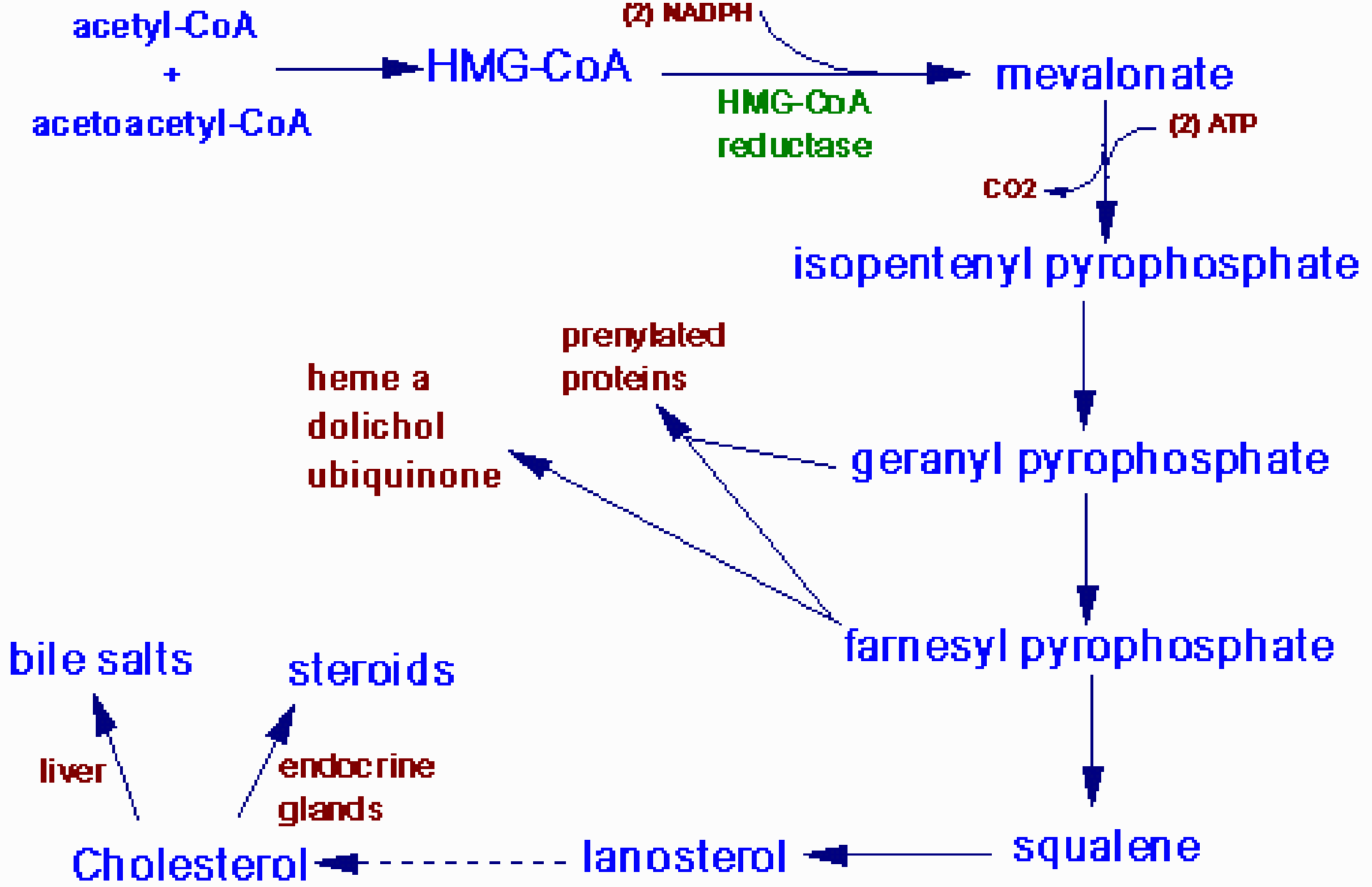
1. Biosynthesis of Mevalonate
2. Formation of Isoprenoid Units
3. Six Isoprenoid Units Form Squalene
4. Formation of Lanosterol
5. Formation of Cholesterol


۲× استیل کوA
تیولاز
استواستیل کوA
HMG-CoA- سنتاز
۳-هیدروکسی- ۳-متیل گلوتاریل- کوA
(HMG-CoA)
HMG-CoA- ردوکتاز
NADPH
NADP
موالونات


2 Acetyl-CoA
THIOLASE
CoA — SH
Acetoacetyl-CoA
H_2O
Acetyl-CoA
HMG-CoA SYNTHASE
CoA — SH
3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA)
Bile acid, cholesterol
2NADPH + $2H^+$
HMG-CoA REDUCTASE
Statins, eg, simvastatin
Mevalonate
$2NADP^+$ + CoA — SH
Mevalonate


Mevalonate
ATP
ADP
Mg2+
MEVALONATE KINASE
Mevalonate 5-phosphate
PHOSPHOMEVALONATE KINASE
ATP
Mg2+
ADP
Mevalonate 3-phospho-5-diphosphate
ADP
ATP
Mg2+
DIPHOSPHOMEVALONATE KINASE
Mevalonate 5-diphosphate
CO2 + PI
DIPHOSPHO-MEVALONATE DECARBOXYLASE
HMG-CoA
trans-Methyl-glutaconate shunt
3,3-Dimethylallyl diphosphate
ISOPENTENYL-DIPHOSPHATE ISOMERASE
Isopentenyl diphosphate
Isopentenyl tRNA
CIS-PRENYL TRANSFERASE
PPI
Geranyl diphosphate
Prenylated proteins
CIS-PRENYL TRANSFERASE
PPI
TRANS-PRENYL TRANSFERASE
CIS-PRENYL TRANSFERASE
Side chain of ubiquinone
Dolichol
Farnesyl diphosphate
Heme a
SQUALENE SYNTHETASE
NADPH + H+
Mg2+, Mn2+
2PPI
NADP+
Squalene


Acetyl-CoA
Mevalonate
Isoprenoid unit
Squalene epoxide
SQUALENE EPOXIDASE
NADPH
FAD
½ O2
X6
Squalene
OXIDOSQUALENE: LANOSTEROL CYCLASE
Lanosterol
NADPH
O2
14-Desmethyl lanosterol
O2, NADPH
NAD+
Zymosterol
ISOMERASE
Δ7,24-Cholestadienol
NADPH
O2
Desmosterol (24-dehydrocholesterol)
NADPH
Δ24-REDUCTASE
Cholesterol
Triparanol



Biosynthesis summary

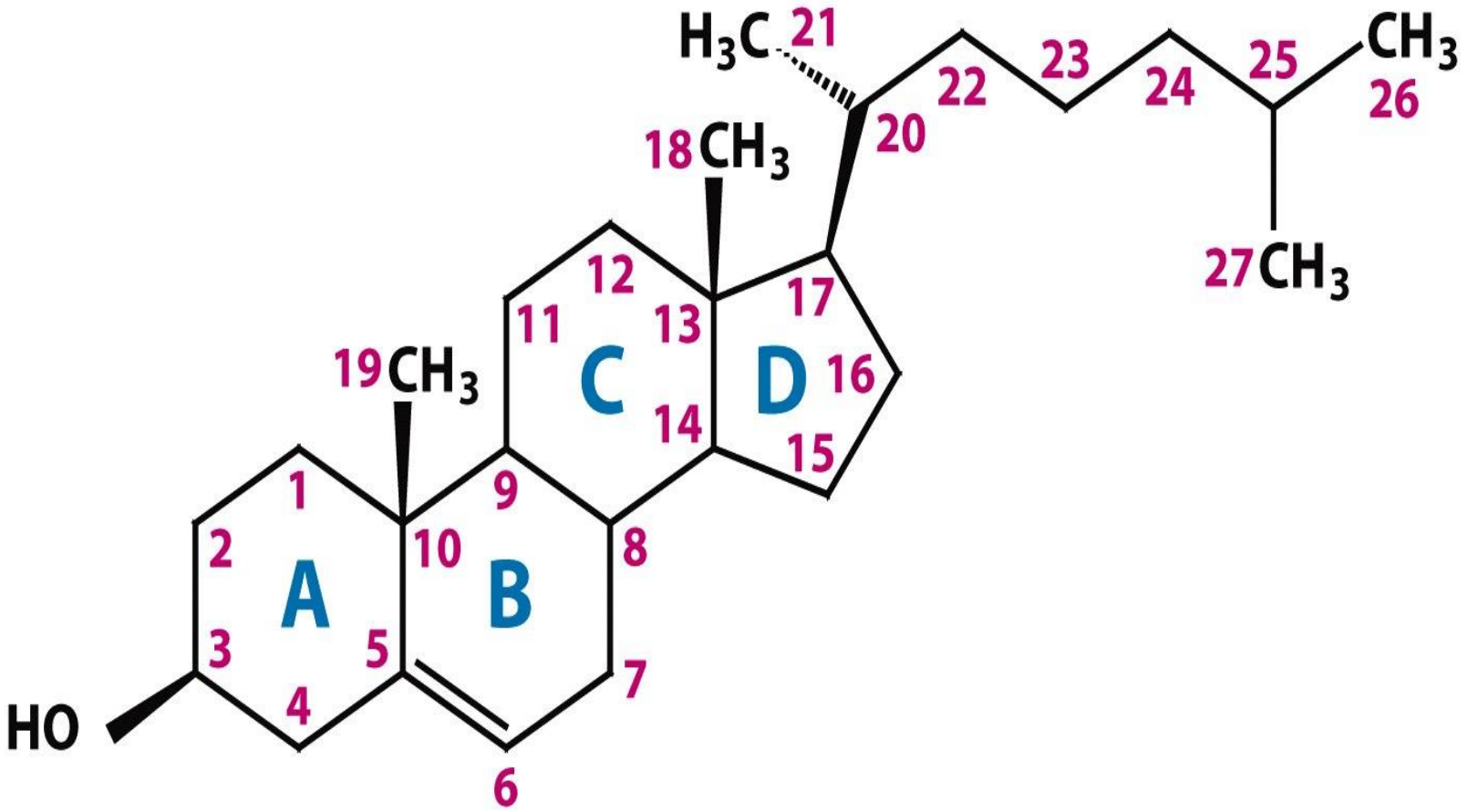


Figure 26-24
Biochemistry, Sixth Edition

Regulation of cholesterol biosynthesis

- HMG CoA reductase is the rate limiting enzyme
- Regulated by:
  - Feedback control by cholesterol itself
  - Hormonal regulation: insulin & glucagon
  - Inhibition by drugs: lovastatin, pravastatin etc

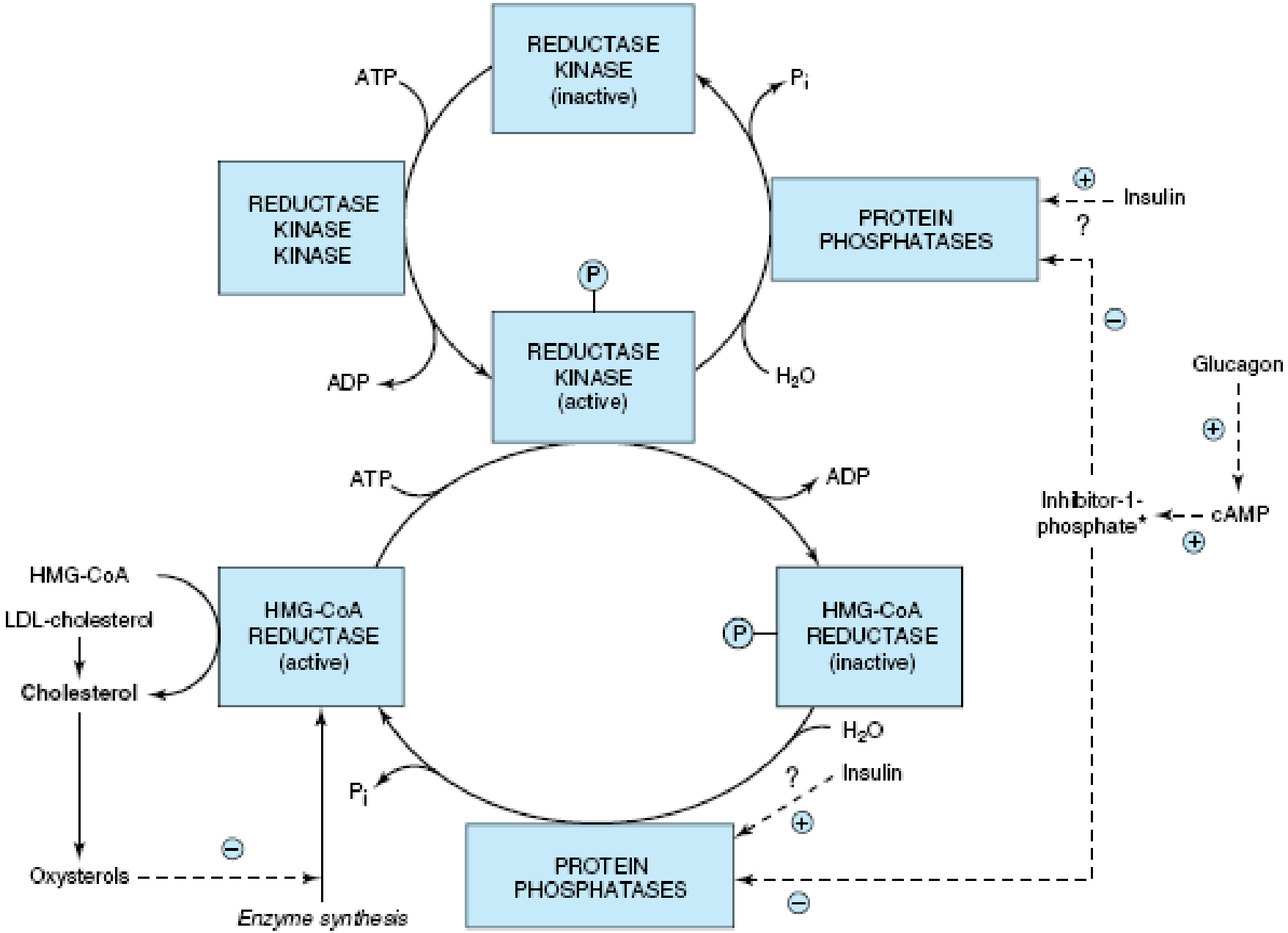


Figure 26–4. Possible mechanisms in the regulation of cholesterol synthesis by HMG-CoA reductase. Insulin has a dominant role compared with glucagon. Asterisk: See Figure 18–6.

Degradation of cholesterol

- Steroid nucleus cannot be degraded to CO_2 and H_2O
- Converted to bile acids
- Serve as the precursor for steroid hormones, vitamin D, coprostanol, cholestanol etc.
- Excreted in stool

تجزیه کلسترول

- سرنوشت کلسترول در کبد
- سرنوشت کلسترول در روده

اسیدهای صفراوی

- ترکیب صفرا
- ساختمان اسیدهای صفراوی
- اهمیت اسیدهای صفراوی
- انواع مهم اسیدهای صفراوی
- سنتز اسیدهای صفراوی
- تنظیم سنتز اسیدهای صفراوی
- عمل فلور روده بر اسیدهای صفراوی
- گردش انتروهپاتیک اسیدهای صفراوی

انواع مهم اسیدهای صفراوی

اسیدهای صفراوی اولیه

- اسید کولیک
  - اسید **گلیکو**کولیک
  - اسید **تورو**کولیک
- اسید کنودزوکسی کولیک
  - اسید **گلیکو**کنودزوکسی کولیک
  - اسید **تورو**کنودزوکسی کولیک

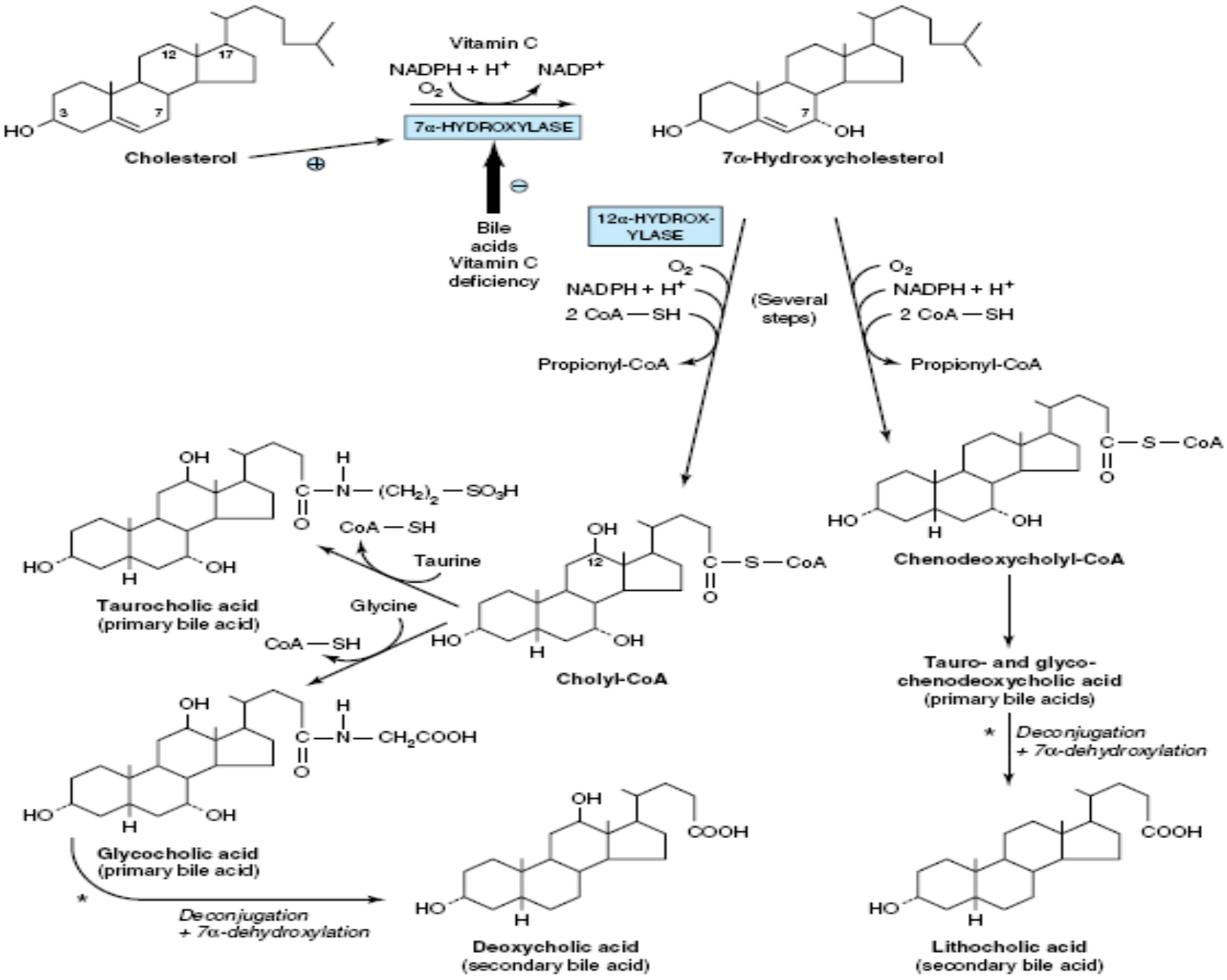


Figure 26–7. Biosynthesis and degradation of bile acids. A second pathway in mitochondria involves hydroxylation of cholesterol by sterol 27-hydroxylase. Asterisk: Catalyzed by microbial enzymes.

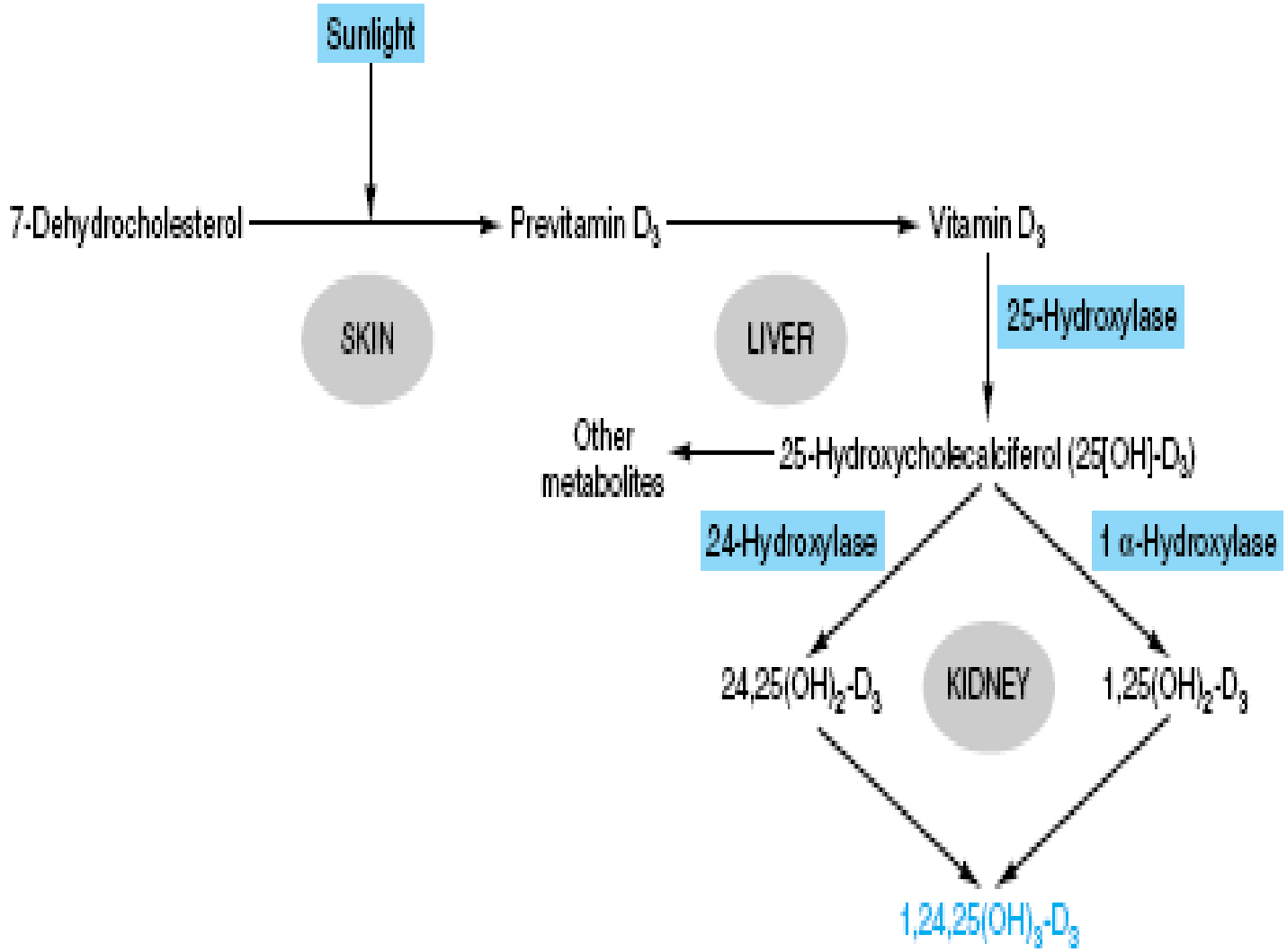
عمل فلور روده بر اسیدهای صفراوی

اسیدهای صفراوی ثانویه

- اسید دزوکسی کولیک
- اسید لیتوکولیک

Use of cholesterol

- Synthesis of bile acids:
- Synthesis of steroid hormones from cholesterol: glucocorticoids, mineralocorticoids, progestins, androgens, estrogens
- Synthesis of vitamin D:


Sunlight
7-Dehydrocholesterol
Previtamin D_3
Vitamin D_3
SKIN
LIVER
25-Hydroxylase
Other metabolites
25-Hydroxycholecalciferol (25[OH]-D_3)
24-Hydroxylase
1 α-Hydroxylase
24,25$(OH)_2$-D_3
KIDNEY
1,25$(OH)_2$-D_3
1,24,25$(OH)_3$-D_3

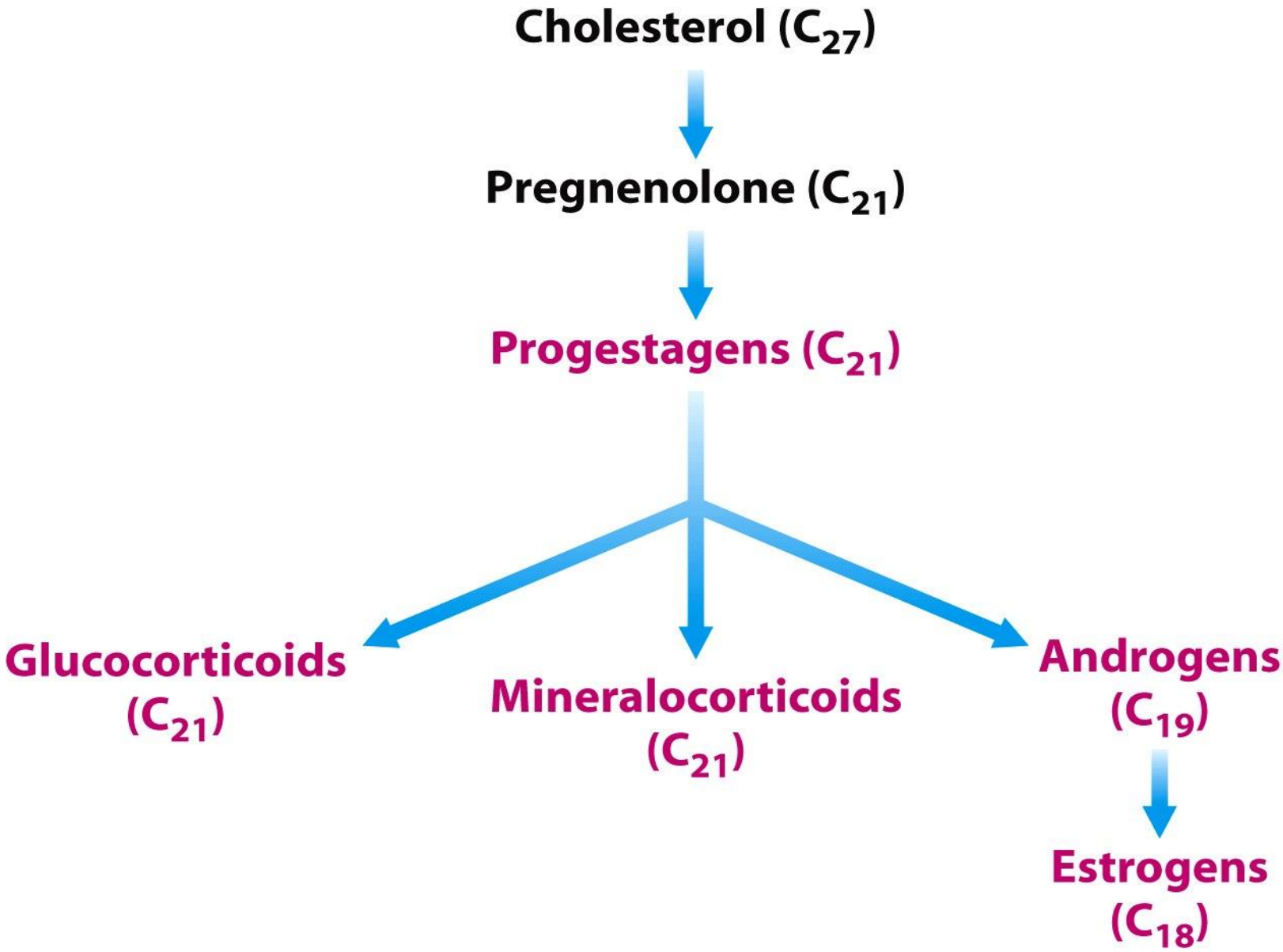
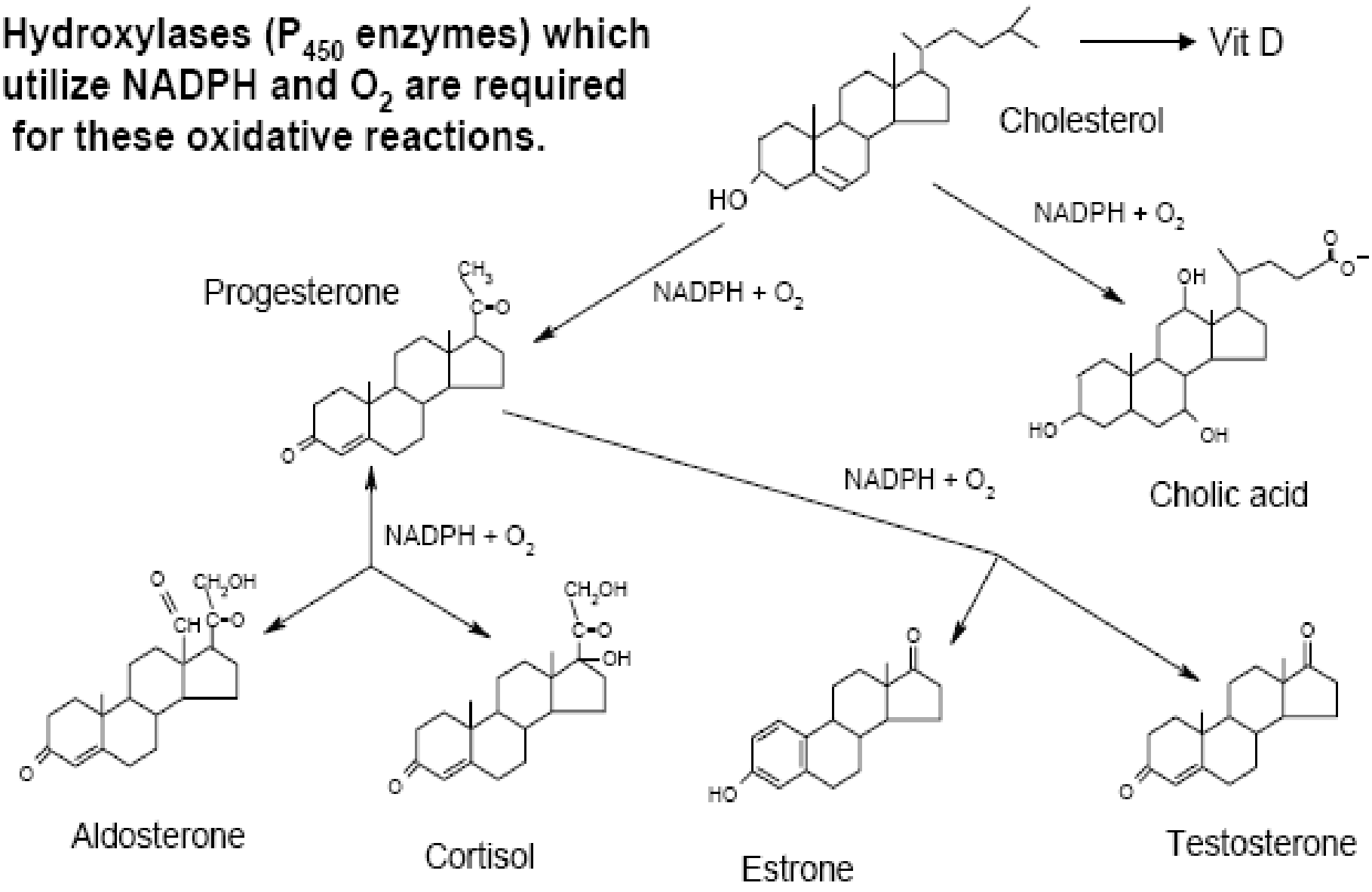


Figure 26-23
Biochemistry, Sixth Edition

Cholesterol Metabolism to Steroids, Bile Acids and Vit D

Hydroxylases (P_{450} enzymes) which utilize NADPH and O_2 are required for these oxidative reactions.



Types of cholesterol lipoproteins

- Total cholesterol: <200mg/dl
- LDL cholesterol: 50-100mg/dl
- HDL cholesterol: >40mg/dl
- VLDL cholesterol: <50 mg/dl

Atherosclerosis

- hardening of the arteries due to the deposition of atheromas
- heart disease is the leading cause of death
- caused by the deposition of cholesteryl esters on the walls of arteries
- atherosclerosis is correlated with high LDL and low HDL

Photograph of an arterial plaque

Frederickson -WHO classification

Type I: incr. chylomicrons, reduced HDL, absence of lipoprotein lipase; deficiency of apo CII (hyperchylomironemia)

Type II-A: raised LDL; decreased catabolism of LDL (receptor deficiency or polygenic)

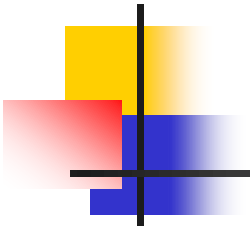
Type II-B: raised VLDL + LDL; often reduced HDL; increased production of VLDL + impaired LDL catabolism

Type III: raised IDL (dysbetalipoproteinemia); abnormal apolipoprotein E; impaired catabolism of IDL; elevated cholesterol and triglycerides (formerly known as broad beta disease)

Frederickson -WHO classification

Type IV: raised VLDL; often reduced HDL; impaired VLDL catabolism; dietary indiscretion (formerly known as hyperprebetalipoproteinemia)

Type V: raised chylomicrons + VLDL; reduced HDL; reduced lipoprotein lipase + VLDL hypersecretion (formerly known as mixed lipemia)



THE END